REMARKS

Applicant hereby affirms the election of restriction group III. Claims 16, and 20-23 are pending. Claims 1-15, and 17-20 were canceled, and new claims 21-24 were added. The new claims are supported by disclosure at page 9, line 26-35, of the specification. Claim 16 was amended to correct a typographical error and to more clearly define the invention; the amendment is supported by disclosure at page 10, line 1, of the specification.

No new matter has been added by this amendment.

The claims were rejected under

35 U.S.C. §112

Claims 16 and 17 were rejected for lack of enablement. On page 5, line 11-18, of Paper No. 7, the Examiner states

> The instant specification does not provide *in vitro* or *in vivo* data showing that increased levels of Mal1 transcript or polypeptide causes reduced plasma glucose and insulin. Furthermore, the specification does not provide *in vitro* or *in vivo* data showing that increased levels of Mal1 transcript or polypeptide renders a predisposition in a mammal to manifest insulin resistance or diabetes. The instant specification does not provide biochemical data demonstrating that there is an established cause-and-effect relationship between increased expression of Mal1 and manifestation or predisposition to insulin resistance or diabetes.

The claimed methods are based on the discovery that a reduction in Mal1 expression by genetic ablation of the gene encoding Mal1 led to increased insulin sensitivity. Knockout mice such as the Mal1 knockout mice described in the specification are valuable tools for discovering the function(s) of genes. This premise is well known and well-accepted in the art. Data obtained from such knockout models establish a "cause-and-effect" relationship between the expression of the gene product and a function of the gene product. In the present case, standard clinical tests

used to evaluate Mal1-deficient mice. For example, the same tests used to diagnose and evaluate insulin resistance and diabetes in humans were used to evaluate Mal1-deficent mice. The biochemical data obtained using such standard glucose tolerance tests, insulin tolerance tests, and measurements of plasma levels of glucose and insulin, showed that a decrease in Mal1 correlated with increased systemic insulin sensitivity. The data also indicated that an increase in Mal1 compared to normal levels is associated with a risk of developing insulin resistance.

A diagnostic test to identify an individual suffering from or at risk of developing a disease need not be based on a "causative factor". Any measurable parameter that changes, the change being correlated with a disease state, provides a valuable marker to identify individuals who may need treatment. For example, existing diagnostic tests for insulin resistance or diabetes (glucose tolerance and insulin tolerance) do not necessarily fit the Examiner's rigid requirement for a diagnostic test, i.e., that the test be based on a firmly established causative factor of the disease. Yet glucose tolerance and insulin tolerance tests are standard assays in evaluating pathologies in insulin/glucose metabolism. The invention provides one more measurable parameter to add to a clinician's arsenal of tools used to identify individuals suffering from or at risk of developing a pathological state.

Applicant therefore submits that the specification coupled with the knowledge in the art of medicine and molecular biology fulfills the requirements of §112 for enablement of the amended claims. Undue experimentation would not be required to practice the claimed methods.

As was reviewed by the Examiner in Paper No. 7, the enablement standard requires that the specification provide a description that, when coupled with the knowledge possessed by a

person of ordinary skill in the art, enables that person to make and use the claimed invention.[1] Enablement is not precluded by the necessity for some experimentation; however, any required experimentation must not be undue experimentation.[2] "The key word is 'undue,' not 'experimentation.'"[3]. The factors to be analyzed in determining whether undue experimentation is required to practice the full scope of the claims are discussed in In re Wands.[4] The court in In re Wands set forth eight factors to be considered in determining whether undue experimentation would be required: (1) the state of the prior art, (2) the predictability or unpredictability of the art, (3) the breadth of the claims (4) the presence or absence of working examples, (5) the amount of direction or guidance presented, (6) the relative skill of those in the prior art, (7) the nature of the invention, and (8) the quantity of experimentation necessary. Applicant's comments will generally track the order in which the Examiner addressed the factors in Paper No.7.

Nature of the invention and state of the prior art

The nature of the invention is a diagnostic assay. The claimed method is not complex. The invention simply requires measuring the amount of a gene product or gene transcript in a tissue sample and comparing it to a normal control value. The format of the assay is common to many diagnostic tests used in clinical medicine.

With respect to the state of the prior art, the Examiner has relied on Pratley et al., a review paper published in 2001. Pratley states that it is not possible to ascertain whether

[1] Atlas Powder Co. v. E.I. duPont De Nemours & Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984).
[2] In re Wands, 858 F. 2d 731, 736-7 (Fed. Cir. 1988).
[3] In re Angstadt, 537 F. 2d 498, 504 (C.C.P.A. 1976).
[4] In re Wands, 858 F.2d 731, 736-7 (Fed. Cir. 1988).

impairments in insulin secretion and insulin action are primary to the development of disease or secondary to metabolic derangements such as mild hyperglycemia. The Examiner then states:

> Since causative factor leading to diabetic disease has not yet been determined, predisposition to diabetes cannot also be determined because the determination of a subject's predisposition to diabetes relies on the evaluation of a causative factor attributing to such a disease, which is, at the time of the filing, not established in the prior art. The art of diabetes pathology and its association to Mal1 expression has not been reported in the prior art at the time of filing.

The claims have been amended to require identifying a risk of developing insulin resistance. As is discussed above, identification of a risk factor need not be based on a causative factor. Indeed, as Pratley states, standard, art-recognized clinical tests such as glucose tolerance and insulin tolerance tests are likely not based on primary or causative factors of diabetes or insulin resistance. Nevertheless, these assays provide valuable information to a clinician with regard to diagnosing disease or identifying individuals who may be at risk of developing a pathologic state.

The association of Mal1 and insulin resistance has not been reported in the art because the discovery is novel and fundamental to the invention. The inventor has made a significant contribution to the art by discovering a new marker, which is useful as another tool with which to evaluate pathologies associated with glucose metabolism.

Predictability or unpredictability of the art

Here, the Examiner states:

> The art of determining a subject's predisposition to manifesting insulin resistance or diabetes is highly unpredictable at the time of filing. Furthermore, the role of Mal1 expression in the manifestation of diabetes or insulin resistance state and predisposition thereto is highly unpredictable at the time of filing.

Applicant has shown that Mal1 expression is linked to insulin resistance. Data from a comprehensive battery of art-recognized tests establish that genetic ablation of Mal1 predictably resulted in decreased body weight, increase systemic insulin sensitivity, and reduced levels of glucose and insulin. The data depicted in Figs. 3A-B of the patent application showed that Mal1 knockout mice have a lower plasma level of glucose and insulin compared to wild type mice using a standard plasma test. Figs. 4 and 5 confirm these data using a standard insulin tolerance test (ITT; Fig. 4) or a standard glucose tolerance test (GTT; Fig. 5). The data indicated that decreased Mal1 expression predictably resulted in increased glucose sensitivity. Mal1-deficient mice were more capable of metabolizing ingested glucose and did so at a faster rate compared to wild type animals. Given that reduced Mal1 levels were consistently correlated with an improved profile of glucose metabolism (i.e., reduced insulin resistance), there is no reason that detection of a higher then normal level of Mal1 would not predictably identify a potential risk of developing insulin resistance.

Breadth of the claims

The claims require measuring the level a specific gene transcript or gene product, Mal1, in a tissue and comparing it to a normal control level to identify an individual at risk of developing insulin resistance. Dependent claims require that the increase in Mal1 be 5, 10, 20, or 50% greater than a normal control value. The scope of the claim is therefore limited to the measurement of one specifically-defined parameter, i.e., a difference in the expression of one gene, in test samples versus a normal control value. The specification teaches how to measure Mal1 expression and provides data from such determinations. The breadth of the claims is

therefore commensurate with the disclosure and teachings provided in the specification of the application.

Presence or absence of working examples

The Examiner acknowledged data in the specification pertaining to decreased bodymass (Fig. 2) and reduced glucose and insulin (Fig. 3). Even more relevant is the correlation of reduced Mal1 with insulin sensitivity, e.g., the data presented in Figs. 4 and 5 (standard insulin tolerance test and glucose tolerance test, respectively). The latter two tests are widely used clinical tests for the evaluation of insulin resistance and abnormalities in glucose metabolism. The data firmly establish the correlation between the level of Mal1 and the insulin resistance. Thus, the examples provided in the specification confirm the premise upon which the claimed assays are based, and establish the reliability and validity of the claimed methods.

The correlation between the level of Mal1 and insulin resistance was confirmed in yet another relevant animal model. As is well known in the art, obesity often leads to insulin resistance. In an animal model of obese mice lacking the gene aP2, a reduction in aP2 was found to confer protection from insulin resistance, i.e., $aP2^{-/-}$ mice had better performance in insulin and glucose tolerance tests compared to obese $aP2^{+/+}$ mice (Uysal et al., 2000, Endocrinology 141:3388-3396; Attachment A). When Mal1 expression was measured in $aP2^{-/-}$ mice, the level of Mal1 was found to be significantly reduced (see Fig. 2C in Makowski et al., 2001, Nature Medicine 7:699-705; Attachment B). These results confirm the data described in the specification and further validate the correlation between Mal1 expression and insulin resistance.

Amount of direction or guidance presented

Regarding level of guidance provided by Applicant, the Examiner commented:

> The instant specification does not provide biochemical data demonstrating that there is an established cause-and-effect relationship or a correlation between increased expression of Mal1 and manifestation or predisposition to insulin resistance or diabetes.

The data obtained from Mal1-deficient mice establish that Mal1 is involved in insulin resistance and shows a correlation between improved glucose metabolism (i.e. reduced insulin resistance) and lower Mal1 levels. The assay to measure Mal1 levels in tissue is straightforward and described on page 9, line 26, to page 10, line 3, of the specification. Figs. 10A and 10B show Mal1 expression in macrophages, and the specification at page 6 line 25, to page 7, line 2, describes methods of evaluating Mal1 expression. Given the simplicity of the assay and the data establishing a correlation between Mal1 level and insulin resistance, Applicant submits that the level of guidance presented in the specification is sufficient for one skilled in the art to carry out the claimed methods without undue experimentation.

Relative skill of those in the prior art

The skilled artisan in the relevant field is a molecular biologist or medical doctor. The field of clinical diagnostic methods, and specifically, methods of detecting abnormalities in glucose metabolism is well developed. Adding one more parameter, i.e., Mal1 level, and using a simple test to measure the amount of Mal1 protein or gene transcript, would be well within the scope of a skilled artisan. The assay is quite simple to perform, and even a clinical lab technician would have little or no difficulty carrying out the assay.

Quantity of Experimentation Necessary

In Wands, the Court stated,

> [A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Applying this criterion here, all of the techniques required to practice the claimed methods were described in the specification or were known to those skilled in the art as of the filing date.

The correlation between insulin resistance and Mal1 expression has been established in two animal models. Contrary to the Examiner's characterization of the claimed methods, Applicant submits that the methods are not complex. The methods simply require the measurement of the expression of one specific gene, i.e., by measuring the amount of a Mal1 gene product or gene transcript. The sequence of the gene and gene product is known and methods of measuring gene transcripts or gene products are also known, e.g., using such standard techniques as northern and western blotting. Thus, Applicant submits that the undue experimentation would not be required of one skilled in the art to practice the claimed invention.

CONCLUSION

On the basis of the foregoing amendments, Applicant respectfully submits that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact either of the undersigned at the telephone number provided below.

A petition for extension of time and a check in the amount of $920.00 is enclosed to

cover the petition fee for a three month extension of time pursuant to 37 C.F.R. § 1.17(a)(3). The Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 21504-044.

Respectfully submitted,

IABeattie

Ingrid A. Beattie, Reg. No. 42,306
Attorneys for Applicants
c/o MINTZ, LEVIN, COHN, FERRIS,
GLOVSKY & POPEO, P.C.
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241

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APPENDIX: MARKED-UP VERSION OF AMENDED CLAIMS

In the claims:

Cancel claim 17. Add new claims 21-24.

16. (amended) A method of diagnosing a risk of developing insulin resistance [or a predisposition thereto] in a mammal, comprising determining the level of Mal1 transcripts or polypeptide in a tissue sample, wherein an increase in the level of said transcripts or said polypeptide in said tissue compared to a normal control tissue indicates that said mammal is at risk of [suffering from or predisposed to] developing insulin resistance.

21. The method of claim 16, wherein said increase is 5% more than a normal control value.

22. The method of claim 16, wherein said increase is 10% more than a normal control value.

23. The method of claim 16, wherein said increase is 20% more than a normal control value.

24. The method of claim 16, wherein said increase is 50% more than a normal control value.